

REMARKS

Claims 30-32, 36-38, 40-49, 51-56, 59-60, 65-68, 72-74, 80-83, 92-109 and 114-119 are in the case.

Reconsideration of this Application and entry of the foregoing amendments are requested. Claims 30-32, 36-38, 45-47, 51-53, 56, 66, 92-97 and 100-103 have been amended in view of the Office Action and claims 114 to 119 are added to better define what the Applicants consider their invention, as fully supported by an enabling disclosure. Additional support for the amendments to these claims can be found, in the previously filed claims.

Election/restriction

The Examiner is of opinion that claims 84-91 and 110-114 constitute non elected subject matter. These claims are therefore withdrawn while reserving the right to file a divisional application covering this subject matter.

New Matter

Claims 46-49, 51, 52, 54, 55, 59 and 60 have been rejected under 35 U.S.C. § 132, first paragraph as introducing new matter into the disclosure. In particular, the Examiner notes that claims 46, 47 and 51 recite negative limitations in their terminal clauses that are not found in the specification. Based on their dependency to claims 46, 47 and 51, claims 48, 49, 52, 54, 55, 59 and 60 are also affected by these negative limitations to the extent that they fail to describe specific methods or products. Applicants respectfully disagree with the Examiner and submit that the terminology "*with the proviso that said substrate [...] is not SKI-1*" does not in fact extend beyond the original disclosure. Support for said terminology may be found throughout the disclosure where it is recognized that it was known that SKI-1 was autocatalytically cleaved (i.e. is its own substrate). See in particular at page 6, lines 1-2; page 28, lines 7-9; and page 46, lines 7-8 which all refer to the "autocatalytic activity" of SKI-1. Although Applicants assume that the objection was directed only against the negative limitation removing SKI-1 as a substrate, for more clarity, Applicants also wish to reiterate that the specification also provides support

for the proviso removing SREPB as a SKI-1 substrate. See in particular page 2, lines 8-16, and page 5, lines 30-33.

REJECTIONS UNDER 35 U.S.C. § 112 FIRST PARAGRAPH

Claims 46-49, 51, 52, 54, 55, 59 and 60 have been rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement. In particular, the Examiner notes that claims 46, 47 and 51 recite negative limitations in their terminal clauses that are not found in the specification. Based on their dependency to claims 46, 47 and 51, claims 48, 49, 52, 54, 55, 59 and 60 are also affected by these negative limitations to the extent that they fail to describe specific methods or products. Applicants refers the Examiner to the response to the objection under 35 U.S.C. § 132 above.

Claims 30-32, 36-38, 40-49, 65, 67, 68, 72-83 and 92-109 have been rejected under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. By each reciting "*defined by ... an amino acid sequence from another mammalian species corresponding to the sequence of*" **all or** part of SEQ ID NO:6 and with a specification that neither defines the degree nor the nature of a recited "correspond[ence]", the Examiner is of the opinion that claims 30, 31, 46, 47 (as well as their dependent claims 32, 36-38, 40-45, 48, 49, 67, 68, 72-83, 92-109) attempt to describe other, as yet unknown, SKI-1 proteases beyond the elected human protease and the two rodent proteases disclosed in the description. The objected wording was removed from the claims. It is thus believed that the rejection of claims 31, 32, 46, 47 and of all claims depending thereon should be withdrawn.

Claim 66 has been rejected under 35 U.S.C. § 112, first paragraph as the specification is not enabling for any embodiment of human protease having an amino acid sequence that diverges from the amino acid sequence of SEQ ID NO: 6 by amino acid substitutions, deletions and insertions, or combinations thereof at as many as 90% of the amino acid positions of SEQ ID NO: 6. The Examiner is of opinion that the specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The amendment to claim 66 is believed to have overcome this rejection.

In view of the above and foregoing, it is respectfully submitted that claims 30, 31, 46, 47, 51, 66 and 92-97, as well as their respective dependent claims comply with 35 U.S.C. § 112, first paragraph.

REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 30-32, 36-38, 40-49, 51, 53, 56, 65-68, 72-83 and 92-109 have been rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. In particular, the Examiner contends that:

1) The Examiner is of opinion that claims 30, 31, 46, 47 and 92-97 (as well as dependent claims 32, 36-38, 40-45, 48, 49, 65-68, 72-83 and 98-109) are not helpful in determining the metes and bounds to which the Applicants intend that the rights to the claimed invention be enforced, since these claims recite ***“defined by...an amino acid sequence from another mammalian species corresponding to the sequence of”*** without defining the degree or nature of a recited “correspond[ence]”. Moreover the same claims are said to be indefinite as they recite ***“defined by...an amino acid sequence from another mammalian species”*** but fail to provide an antecedent basis for *“another species”*. The Examiner is referred to Applicant’s above response to the § 112, first paragraph rejection.

2) The Examiner rejects claim 30 (as well as dependent claims 36, 40-45, 65, 72 and 80-83) as being indefinite in reciting *“enzymatically active”*, because where an activity is disclosed, i.e. proteolysis, the use of the generic term *“enzymatically”* is ambiguous. Applicants have therefore amended claim 30 by deleting the word *“enzymatically”*;

3) The Examiner rejects claim 32 as being indefinite in reciting *“said part has a molecular weight of about 14 kDa”*, since the fragment of claim 31 has no specific amino acid sequence by which a molecular mass can be calculated. Claim 32 was amended to replace the term “part” by the term “fragment”. The Examiner then suggested that claim 32 indicates how a mass of “about 14 kDa” is determined.

Claim 14 now recites how the mass is determined and support for this amendment is provided at page 13, lines 30-33. Claim 32 (as well as dependent claims 38, 68 and 74) is further rejected as being indefinite because of the term "*tight*". This term was removed from claim 32 in order to accelerate prosecution. Finally, the Examiner is of opinion that the expression "*in a cell growth*" should be defined in claim 45. The term "cell growth" was removed pursuant to the Examiner's request and in order to accelerate prosecution.

4) The Examiner rejects claims 51, 53 and 56 as each being indefinite where none recites sequence identifiers for the amino acid sequences of the peptides they recite. Sequence identifiers were therefore included in the claims and a new sequence listing submitted comprising new sequences 77 and 78 corresponding to the sequence recited in claims 53 and 56, and that recited in the proviso of claim 51. The Examiner believes that claim 46 is indefinite in reciting "*contacting said substrate*" in clause (a) and then inserting a proviso excluding known substrates, because it leaves the nature of what is intended to be a substrate ambiguous. It is respectfully submitted that known substrates other than SKI-1 and SREBP, exist for the enzyme, for e.g. pro-BDNF, see page 5, line 30. It is further submitted that the Applicants present a generic formula in claim 51 for selecting an appropriate substrate for SKI-1. Finally, claim 66 is rejected as being indefinite in reciting "*at least 70% homology*", because it fails to indicate the nature of the nucleotide sequence homology intended, rendering the scope of the claim ambiguous. The amendment to claim 66 is believed to have overcome this rejection.

In view of the above and foregoing, it is respectfully requested that these objections under 35 U.S.C. § 112, second paragraph be withdrawn.

REJECTION UNDER 35 U.S.C. § 102

Claims 30-32, 36-38, 40-47, 51-52, 54, 55, 65-68, 72-83, 92-97, and 104-109 have been rejected as being anticipated by **Brown et al.** (U.S. 6,322,962, hereinafter "**Brown**") under 35 U.S.C. § 102(e).

The Examiner notes that the introduction of the claim limitation "*defined by ... an amino acid sequence from another mammalian species corresponding to the sequence of*" can be considered to embrace any functionally-equivalent

protease, or fragmentary protease disclosed in *Brown*, thus the rejections of claims 30-31, 46-47, 65, as well as their dependent claims 32, 36-38, 40-45, 48-49, 67-68, 72-83 and 92-109. The Examiner further alleges that *Brown's* SEQ ID NO: 3 of a human Site-1 protease is identical to the amino acid sequence of the human SKI-1 protease set forth in SEQ ID NO: 6 of the present application. The Examiner also contends that the disclosures in *Brown et al.* of manipulations of, expression of, proteolytic activity of, and substrate recognition of, a hamster SKI-1 protease, which corresponds to the human protease, anticipate manipulations of, expression of, proteolytic activity of, and substrate recognition of, a human SKI-1 protease. The Examiner also contends that *Brown et al.* discloses polynucleotides encoding a soluble, truncated SKI-1 and recombinant vectors and cells transformed therewith and methods for preparing same.

The objected wording "*defined by ... an amino acid sequence from another mammalian species corresponding to the sequence of*" was removed of the claims and this amendment is believed to overcome the objection with regards to claims 32, 36-38, 40-45, 48-49, 67-68 and 72-83, as indicated above.

The Examiner alleges that claims 104 to 108 are anticipated by *Brown et al.* because they "disclose that the SKI-1 prodomain fragment is secreted in the medium". Claims 92 to 109 recite human SKI fragments of 1 to 169, 1 to 188 or 1 to 197; and 17-169, 17-188 or 17-197, compositions comprising same and isolated nucleic acid encoding same. It is respectfully submitted that *Brown et al.* does not disclose any such fragment. Indeed *Brown* indicates that the hamster SKI-1 is first cleaved to generate a S1P-A inactive fragment of 23-1052 (col. 16, lines 31-33). This S1P-A is then autocatalytically cleaved at Site-B to produce the 138-1052 fragment S1P-B which cleavage liberates the 115 amino-acid 23-137 fragment (col. 16, lines 33-37). The S1P-B fragment is then cleaved to produce a 187-1052 fragment (col. 16, lines 39-41). It is respectfully submitted thus that the only prodomain fragment disclosed by *Brown* is the "115 amino-acid propeptide that is secreted intact into the medium" (Col. 16, lines 33-37), namely a 23-137 fragment. This disclosure does not anticipate or suggest the claimed fragments, compositions and nucleic acids of the present invention which are recombinant human SKI fragments.

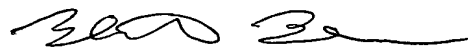
The Examiner further alleges that *Brown* also anticipates claims 31-33, 67-69 and 92-97 in disclosing a peptide having an amino-terminus at about 18 and a carboxyl-terminus at position 137 which is secreted into the culture medium. It is believed, since claims 33 and 69 are cancelled that the Examiner meant to say 31-32 and 67-68. Brown discloses a hamster 115 amino-acid fragment, namely a 23-137 fragment (Col. 16, lines 33-37) rather than one having an amino-terminus at position 18. The objected wording "*defined by ... an amino acid sequence from another mammalian species corresponding to the sequence of*" was nevertheless removed and this objection is believed to have been overcome.

The Examiner is of further opinion that Brown *et al.* discloses the peptides of claims 51-52, 54 and 55, notably the peptide as set forth in SEQ ID NO: 55 of Brown *et al.* It is respectfully reiterated that the amino sequence of SEQ ID NO: 55 is a part of a SREBP-2 (see page 53, line 24-25 of the present application, and col. 71, lines 11 to 14 of Brown *et al.*). Claims 51, and therefore claims 52, 54, 55, 59 and 60 depending therefrom, expressly exclude a "a sterol-regulatory element-binding protein (SREBP) **or a part thereof**". It is further reiterated that this proviso is supported by the application as filed. The Applicants expressly admitted in the application that SREBP, and therefore any part thereof containing the SKI cleavage site in this fragment was a known substrate for SKI. See in particular page 2, lines 8-16, and page 5, lines 30-33 of the present application.

The rejections of the original claims are believed to have been overcome by the present remarks and the introduction of new claims. From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order, and such an action is earnestly solicited.

Authorization is hereby given to charge deposit account no. 17-0055 for any deficiencies or overages in connection with this response.

Respectfully submitted,



Zhibin Ren
Registration No. 47,897
Quarles & Brady LLP
411 East Wisconsin Avenue
Milwaukee, Wisconsin 53202-4497

Tel: 414-277-5633
Fax: 414-978-8663
QBMKE\5654400.1